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EXAMINER	
DAVIS, MINH TAM B	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,226	BOSCH, MARNIX L	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 13-32, species: 1) BCG and interferon gamma, or LPS, TNF-alpha as maturing agent, and 2) CD86 or CD80 co-stimulatory molecule are examined in the instant application.

Withdrawn Rejection

The 112, second paragraph has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5,13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, for reasons already of record in paper of 10/22/09.

The response asserts as follows:

Applicants must strongly disagree with the rejection of claims 1-3, 5 and 13 under 35 U.S.C. § 102(a) as being anticipated by Triozzi et al. and as evidenced by Labeur et aL In particular, contrary to the allegation by the Examiner the specification as filed does not teach that GM-CSF and IL-4 are maturation agents. While the Examiner is correct, a sentence appears at

page 11, second paragraph, listing GM-CSF and IL-4 as maturation agents, the statement is merely a typographical and/or clerical error that would be recognized by the skilled artisan. The combination of GM-CSF and IL-4 is clearly defined as one of several differentiation agents for certain dendritic precursor cells. See for example, page 2, lines 28-30 ("DCs exist in peripheral tissues in an immature form, ready to take up and process antigen. It is this immature cell that is most closely mimicked by the DCs generated from monocytes in the presence of GM-CSF and IL-4."), page 6, line 19 through page 10, line 7 (In particular page 9, lines 16-27, wherein GM-CSF and IL-4 are described as dendritic cell differentiation agents.), page 11, lines 1-4, and the examples. Dendritic cell maturation agents are defined in the specification as filed at, for example, page 10, lines 8-27. Still further, the characteristics of, and differences between, immature and mature DCs can be found in the specification at page 11, lines 16-30. The Examples in the specification show that murine bone marrow dendritic cell precursors are clearly different than the dendritic cells treated with a dendritic cell maturation agent. In particular, example 1 shows that monocytic dendritic dell precursors isolated by tangential flow filtration and differentiated in GM-CSF alone and subsequently contacted with the dendritic cell maturation agents BCG and IFNy differ in their ability to uptake and process tumor cell antigen. See page 15, Table 1. Further, Examples 2 and 3 show that murine bone marrow cells, subsequent to red cell lysis, and incubated with murine GM-CSF and IL-4 did not resolve xenogenic tumor as well as similar differentiated bone marrow cells subsequently partially matured with BCG and IFNy. Applicants clearly did not intend the combination of GM-CSF and IL-4 to be considered dendritic cell maturation agents as alleged by the Examiner.

As such, Applicants prior argument regarding Triozzi et aL and Labeur et al. are relevant to the present rejection. In particular, Triozzi et al. do not use partially mature dendritic cells in the methods disclosed, but instead use immature dendritic cells differentiated from monocytes by culture in GM-CSF and IL-4. This method of generating immature dendritic cells from monocytes is well known to the skilled artisan. For example, Sallusto and Lanzavecchia, J. Exp. Med. 179:1109-1118, 1994, clearly demonstrated that monocytes when cultured in the presence of GM-CSF and IL-4 differentiate into immature dendritic cells. In addition, as above, the present specification demonstrates that murine bone marrow cells, cultured in the presence of GM-CSF and IL-4 are not the same as those same cells contacted with a dendritic cell maturation agent in regard to ability to uptake tumor antigen or ability to reduce the growth of xenogenic tumor when administered to a mouse.

Labeur et al. cited by the Examiner does not conflict with the teaching of Sallusto and Lanzavecchia. In particular, Labeur et al. induce the differentiation of dendritic cells from murine bone marrow dendritic cell precursors. It is well known in the art that the cytokines necessary to induce the differentiation of human immature dendritic cells and/or human mature dendritic cells from human monocytic dendritic cell precursors are different from those necessary to induce differentiation of murine immature dendritic cells and/or murine mature dendritic cells from murine bone marrow dendritic cell precursors. Labeur et al. demonstrate that bone marrow dendritic cell precursors from mice are induced to differentiate into immature dendritic cells by culture in GM-CSF alone. Culture of the bone marrow dendritic cell precursors in GM-CSF and IL-4 induced the cells to differentiate and mature as measured by cell surface phenotype and the substantial reduction in phagocytosis and endocytosis. The phenotype of

dendritic cells produced by Labeur et al. by culture in GM-CSF and IL-4 differ only in the stimulus of mixed lymphocyte reactions and efficiency of in vitro peptide presentation when compared with bone marrow dendritic cell precursors cultured in the presence of GM-CSF and IL-4 with TNF-alpha, LPS or CD40L. Labeur et al. specifically state that IL-4 "is a potent enhancer of mouse DC maturation". See page 173, right column, last paragraph, lines 6-7. As such, Labeur et al. does nothing to support the characterization by the Examiner of the dendritic cells used by Triozzi et al. being partially mature dendritic cells.

In addition, the Examiner has noted that "fully mature DCs exposed to GM-CSF plus IL-4 and CD40L, taught by Labeur et al(Labeur et al., abstract), that have the ability to pick up and process antigen, are interpreted as partially matured DCs. Applicant has reviewed the abstract of Labeur et al. and only find the following statements regarding intermediate dendritic cell maturation: "Whereas cells cultured in GM-CSF alone were functionally immature, cells incubated in CD40L or LPS were mature BmDC, as evident by morphology, capacity to internalize Ag, migration into regional lymph nodes, IL-12 secretion, and alloantigen or peptide Ag presentation in vitro. The remaining cultures exhibited intermediate dendritic cell maturation." See Labeur et al. abstract, lines 6-9. Applicant strongly disagrees that this statement supports the Examiner's conclusion that the DCs produced by Labeur et al. have the ability to pick up and process antigen and therefore should be interpreted to be partially mature DCs. In fact, Labeur et aL teach that bone marrow DCs induced by culture in GM-CSF and IL-4 do not retain the ability to take up and process antigen. Table II, at page 171, clearly shows that BmDCs cultured in GM-CSF and IL-4 have a substantially reduced ability to uptake antigen and have essentially the same capacity for phagocytosis as those BmDCs cultured in the presence of GM-

CSF and IL-4 plus LPS or CD40L. At page 171, right had paragraph beginning at line 1 of the text, the authors explain the data as follows: "Incubation of cells with IL-4 resulted in a marked down regulation of FITC-E. coli uptake. Further addition of Flt3L, TNF-a, CD40L, or LPS did not have additional effects on phagocytosis". As such, even if the culture of monocytic dendritic cell precursor cells in GM-CSF and IL-4 could be directly compared with the culture of murine bone marrow dendritic cell precursor cells in GM-CSF and IL-4, the teachings of Labeur et al. are not supportive of the conclusion of the Examiner that the dendritic cells of Labeur et al. or Torizzi et aL are partially mature dendritic cells as defined and used in the present application and claims. Finally, Applicant shows in the Examples presented in the specification as filed that murine bone marrow cells cultured in the presence of GM-CSF and IL-4 differ in their ability to uptake and process tumor antigen when compared with murine bone marrow cells partially matured by contact with BCG and IFN-gamma.

The response has been considered but is not found to be persuasive for the following reasons:

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See ln re Van Geuns. 988 F.2d 1181, 26 USPQZd 1057 (Fed. Cir. 1993).

Further, the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al is reasonably interpreted as partially matured dendritic cells, because the language "partially matured dendritic cells" is a relative term, and because Labeur et al clearly teach that: 1) murine DCs treated in GM-CSF and IL-4 have **intermediate degree** in maturation, in between the immature murine DCs treated only with GM-CSF and the more mature DCs treated in GM-CSF

and IL-4 plus LPS or CD40L (p.173, second column, last paragraph, **lines 8-11**), and 2) those murine DCs treated with GM-CSF and IL-4 have the ability to take up and process antigen, in addition to antigen presentation, and T cells stimulation (p.168, second column, second paragraph, p.171, second column, second paragraph, figure 2 on page 172, figure 3 on page 172 and figure 4 on page 173). That is, Figure 3 and p.171, second column in Labeur et al show that when incubated with an antigen, the OVA peptide, murine DCs treated with GM-CSF and IL-4 are **intermediate** between immature DCs treated GM-CSF alone and more matured DCs treated with GM-CSF and IL-4 plus LPS or CD40L **in the ability to present the antigen**.

In addition, the response does not have any objective evidence or references showing that induction of intermediate maturity of dendritic cells from murine bone marrow by GM-CSF and IL-4, as taught by Labeur et al, would not apply to dendritic cells from murine or human monocytes. Contrary to the response assertions, Labeur et al teach that in agreement with other published investigation of **human DC**, one of which is Sallusto et al, 1994, which teach human monocytes (reference 9), this combination of cytokines provide good conditions for generation of cells with the characteristic phenotype and functional properties of DC in the murine system (Labeur et al, p.173, last paragraph, lines 17-20).

Further, Table II at page 171 of Labeur et al only discloses phagocytotic activity of different treated murine DCs. The ability to take up and process antigen by murine DCs treated with GM-CSF and IL-4 is actually shown in figure 3 and p.171, second column, item under "Allostimulatory activity and presentation of OVA peptide". Figure 3 and p.171, second column in Labeur et al show that when **incubated with an antigen**, the OVA peptide, murine DCs treated with GM-CSF and IL-4 is intermediate between immature murine DCs treated GM-CSF

alone and more matured murine DCs treated with GM-CSF and IL-4 plus LPS or CD40L in the ability to present the antigen. In other words, those murine DCs taught by Labeur et al must inherently have been able to pick up and process the antigen present in the incubation medium, in order to present the antigen. This ability of picking up and processing the antigen necessary for presenting the antigen, however, is lost in fully mature, i.e., terminally differentiated DCs, as defined in the instant specification (p.11, paragraph before last).

Concerning the assertion that the Examples presented in the specification as filed show that murine bone marrow cells cultured in the presence of GM-CSF and IL-4 differ in their ability to uptake and process tumor antigen when compared with murine bone marrow cells partially matured by contact with BCG and IFN-gamma, the limitation of BCG and IFN-gamma is not in the claims 1-3, 5, 13.

Although Triozzi et al do not explicitly name the dendritic cells treated with GM-CSF and IL-4 as partially matured dendritic cells, however, the claimed partially matured dendritic cells appears to be the same as the prior art dendritic cells. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 2, 4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, **in view of** Labeur et al, 1999, J Immunol, 162: 168-175, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record of paper of 10/22/09.

The response asserts as follows:

Applicant strongly disagrees with the allegations and assertions of the Examiner. As above, Triozzi et al. do not teach the administration of partially mature DCs, but instead teach the administration of immature DCs differentiated from monocytic dendritic cell precursors by he standard method of culturing the monocytic dendritic cell precursors in the presence of GM-CSF and IL-4. Labeur et aL do not add anything to the disclose of Triozzi et al. that discloses or suggests either the administration of partially mature dendritic cells to a patient or the use of

partially mature DCs isolated or differentiated from precursor cells isolated from any source. As above, Labeur et al. teach that murine bone marrow dendritic cell precursors cultured in the presence of GM-CSF and IL-4 differentiate into dendritic cells that have a significantly reduced ability to up take and process soluble antigen. The dendritic cells produced by the method of Labeur et al. also differ in their ability to induce an anti-tumor response when compared with bone marrow dendritic cell precursor maturation agents, such as LPS or CD40L, but not in the ability to up take and process antigen. The specification also shows in the Examples that murine bone marrow dendritic precursor cells cultured in the presence of GM-CSF and IL-4 are different from those subsequently cultured in the presence of a dendritic cell maturation agent as defined in the present specification. Table 1 of the specification shows that bone marrow dendritic precursors cells cultured in the presence of a dendritic cell maturation agent subsequent to culture in GM-CSF and IL-4 were better at antigen uptake as measured by either the percentage of cells that take up antigen or by the amount of material picked up.

The addition of Murphy et al. adds nothing to provide the missing elements from Triozzi et aL and/or Labeur et aL when consider either alone or in any combination. Therefore, as the Examiner has failed to establish aprimafacie case for obviousness Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 2 and 4 as being unpatentable over Triozzi et al. in view of Labeur et aL, and further in view of Murphy et al.

The response has been considered but is not found to be persuasive for the following reasons:

The dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al, and as evidenced by Labeur et al appear to be the same as the claimed partially matured dendritic cells, supra.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to obtain the DCs taught by Triozzi et al and Labeur et al from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood, as taught by Murphy et al, to increase the number of available sources for making DCs.

It would have been obvious to replace DCs obtained from the individual to be treated, taught by Triozzi et al and Labeur et al with DCs isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

2. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07 in view of Labeur et al, 1999, J Immunol, 162: 168-175, and further in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07) for reasons already of record in paper of 10/22/09.

The response asserts as follows:

Applicant again must strongly disagree with the allegations and assertions of the Examiner. In particular, as above, Triozzi et al. does not disclose or suggest a method of administering partially mature DCs that have not been contacted with antigen in vitro. In addition, Labeur et al. also do not disclose or suggest such a method. Further, Bosch et al. and/or Chakraborty et al. do not disclose or suggest any element missing from the teachings of Labeur et al. to render obvious any of claims 1 and 6-9. Even if either Bosch et al. and/or Chakraborty et al. were to teach or suggest those elements alleged by the Examiner above, any combination of those references with Triozzi et al. and/or Labeur et al. either alone or in any combination would not result in the present invention. If the references were combined as suggested by the Examiner, at most, the skilled artisan might use a maturation agent suggested by Bosch et al. to mature DCs that had been exposed to antigen prior to administration to a subject. That is not the invention as recited in any of claims 6 through 9. The addition of Chakraborty et al., which is alleged by the Examiner to teach the secretion of IL-12 by certain dendritic cells, provides nothing that would disclose or suggest the present invention. In particular, Chakraborty et al. provides no information about how dendritic cells that have not been allowed to complete maturation would respond when administered to a patient. As such, neither Triozzi et al. and/or Labeur et al. when considered alone or in any combination with Bosch et al. and/or Chakraborty et al. do not disclose or suggest the invention as recited in claims 6 through 9.

The response has been considered but is not found to be persuasive for the following reasons:

The dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al, and as evidenced by Labeur et al appear to be the same as the claimed partially matured dendritic cells, supra.

Although Bosch et al use treated DCs that have been exposed to antigen prior to their administration to a subject, the primary reference, Triozzi et al, teach the use of treated DCs for administration into a cancer patient, without the need of their exposure to a cancer antigen, prior to their administration to the patient.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to add to GM-CSF plus IL-4 maturing agent taught by Triozzi et al and Labeur et al with BCG and interferon gamma, as taught by Bosch et al, in the method taught by Triozzi et al and Labeur et al for maturing DCs in vitro for use in producing an anti-cancer response, because BCG and interferon gamma as maturing agent as taught by Bosch et al would be advantageous, in view that they selectively enhance the production of stimulating DCs that secrete IL-12, and therefore efficiently stimulating T cells, in view of the teaching of Chakraborty et al, and promoting anti-tumor immunity, in view of the teaching of Labeur et al.

3. Claims 14-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07 in view of Labeur et al, 1999, J Immunol, 162: 168-175, for reasons already of record in paper of 10/22/09.

The response asserts as follows:

Applicant again must disagree with the allegations and assertions of the Examiner. The partially mature DCs of the present claims are not the same as those taught by Triozzi et al. GM-

CSF and IL-4 are not considered dendritic cell maturation agents by Applicant as set forth above. Further, as above, Example 1 clearly shows that murine bone marrow dendritic precursor cells contact with GM-CSF and IL-4 are not the same as those additionally matured in the presence of a dendritic cell maturation agent, such as a combination of BCG and IFNy. In addition, Triozzi et al. and/or Labeur et al. when considered alone or in any combination do not disclose or suggest a method wherein partially matured dendritic cells are administered by any method. Further, contrary to the Examiners allegations, it would not have been obvious to one of ordinary skill to choose direct administration of the presently claimed partially matured DCs over subcutaneous injection. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) of claims 14 through 18 as being unpatentable over Triozzi et al. in view of Labeur et al. be withdrawn.

The response has been considered but is not found to be persuasive for the following reasons:

The dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al, and as evidenced by Labeur et al appear to be the same as the claimed partially matured dendritic cells, supra.

Further, it would have been obvious to one of ordinary skill to choose direct administration of the partially matured DCs taught by Triozzi et al, as evidenced by Labeur et al, over subcutaneous injection, because DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice, as taught by Labeur et al.

4. Claims 19-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07 in view of Labeur et al, 1999, J Immunol, 162: 168-175, and further in view of Nikitina et al, 2001, Int J Cancer, 94: 825-833, IDS# AN of 05/09/07, for reasons already of record in paper of 10/22/09.

The response asserts as follows:

Applicant must again respectfully disagree with the allegations and assertions of the Examiner. As set forth above, the partially mature DCs of the present claims are not the same as those taught by Triozzi et al. GM-CSF and IL-4 are not considered dendritic cell maturation agents by Applicant as set forth above. Further, as above, Example 1 clearly shows that murine bone marrow dendritic precursor cells contact with GM-CSF and IL-4 are not the same as those additionally matured in the presence of a dendritic cell maturation agent, such as a combination of BCG and IFNy. In addition, Triozzi et al. and/or Labeur et al. when considered either alone or in any combination do not teach the methods or compositions of the present claims. In particular, Triozzi et al. does not teach the administration of partially matured DCs, but only teaches the administration of immature DCs that lose their ability to induce an immune response when administered. In addition, the DCs taught in Labeur et al. are exposed to antigen in vitro prior to administration to an individual and are not the same as the DCs used in the presently claimed methods. Thus, Applicant submits that Triozzi et al. and/or Labeur et al. even if combined with Nikitina et al. fail to teach or suggest each and every element of claims 19 and 20. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) of claims 19 and 20 as being unpatentable over Triozzi et al. in view of Labeur et al. in further view ofNikitina et al. be withdrawn.

The response has been considered but is not found to be persuasive for the following reasons:

The dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al, and as evidenced by Labeur et al appear to be the same as the claimed partially matured dendritic cells, supra.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to combine DCs administration taught by Triozzi et al and Labeur et al with radiation therapy, because gamma irradiation induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina et al.

5. Claims 21-23, 25, 27-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, in view of Labeur et al, 1999, J Immunol, 162: 168-175, and Sukhatme et al (US 6,797,488), for reasons already of record in paper of 10/22/09.

The response asserts as follows:

Applicant must again respectfully disagree with the rejection of the Examiner. The dendritic cells of the present invention are not the same as those of the cited prior art in spite of the passage in the instant specification cited by the Examiner. As above, the passage in the instant specification is clearly an obvious typographical and/or clerical error. The remainder of the specification fully distinguishes the prior art from the partially mature DCs of the present application. In particular, the dendritic cells of Triozzi et aL are immature dendritic cells and are

not partially matured dendritic cells as set forth in claims 21-23, 25 and 27-32. As set forth in the specification at page 9, line 28 through page 10, line 7 and page 11, lines 5 through 30, immature dendritic cells and partially mature dendritic cells differ in a number of ways including the levels of expression of a number of cell surface antigens CD80 and CD86 recited in the claims. As well as the cell surface molecules CD 14, CD 11 c not recited in the claims. In addition, mature and immature DCs differ in the phosphorylation level of a number of intracellular proteins including for example, jak2. Applicant respectfully directs the Examiner to additional differences in the cell surface phenotype and the levels of IL-10 and/or IL-12 produce by monocytic dendritic cell precursors cultured in the present of GM-CSF and IL-4 and those cultured in the presence of GM-CSF, IL-4 and a dendritic cell maturation agent. Immature dendritic cells induced to mature by the addition of, in this example, IFNy and SAC are clearly different in the amounts ofIL-10 and/or IL-12 produced and in cell surface phenotype. As such, it is clear that the "partially mature" dendritic cells, immature dendritic cells contacted with a dendritic cell maturation agent, as recited in the present claims reciting the cell surface markers CD80 and CD86 do not have the same properties as the dendritic cells of either Labeur et al. or Triozzi et al. Applicant also again respectfully directs the Examiner to page 2652, right column, lines 2 through 11 of Triozzi et al. where the authors conclude that the immature dendritic cells administered in vivo lost the co-stimulatory molecule B7-2 (CD86A) and showed a decrease in the intensity of CD 11 c suggesting the possibility that immunostimulatory activity typical of dendritic cells was down regulated. Applicant discloses in the specification as filed that the "partially matured" dendritic cells, as claimed, down regulate cytokine receptors on the surface as compared with "immature" dendritic cells making them less sensitive or responsive to any immunosuppressive effects of

cytokines in the intratumoral space. Immature dendritic cells as defined in the specification include monocytic dendritic cells cultured in the presence of GM- CSF and IL-4. As such, the "partially matured" dendritic cells of claims 21 through 23 and 27 through 32 are not the same as those taught by Triozzi et al. Sukhatme et al. is cited by the Examiner as disclosing a pharmaceutical carrier. As Triozzi et al. and/or Labeur et aL do not teach the "partially mature" dendritic cells of the present invention or methods for their administration, the addition of the teachings of Sukhatme et al. does not disclose or suggest the present invention.

The response has been considered but is not found to be persuasive for the following reasons:

The dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al, and as evidenced by Labeur et al appear to be the same as the claimed partially matured dendritic cells, supra.

DCs generated in vitro by GM-CSF and IL-4 taught by the art express the same elected co-stimulatory molecules **CD80 and CD86** as claimed in claim 22 (p.2649, first column, item under Results). Further, other than the elected CD80 and CD86 cited in claim 22, the limitation of other surface antigens, CD14, CD11c, the phosphorylation level of a number of intracellular protein, including for example, jak2, the amounts of IL-10 and /or IL-12, the down regulation of cytokine receptors on cell surface is not recited in the claims, and therefore the arguments are moot.

6. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, in view of Labeur et al, 1999, J Immunol,

162: 168-175, of record, and Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record in paper of 10/22/09.

The response asserts as follows:

Applicant must again disagree with the Examiner. As above, the cited primary references Triozzi et al. as demonstrated in Labeur et aL are not the same as the claimed partially mature DCs. The partially mature DCs as set forth in the present specification and claims have been induced in vitro to begin maturation with a DC maturation agent, not GM-CSF and IL-4. In Triozzi et al. immature monocytic derived dendritic cells are administered to a patient, or Labeur et al. where DCs contacted with antigen and that have been induced to full maturation as indicated by their substantial loss of the ability to uptake antigen in vitro are administered to patients. As such, Triozzi et al. and/or Labeur et al. when either considered alone or in combination teach neither the administration of partially mature DCs or compositions that comprise partially mature DCs combined with a pharmaceutically carrier, much less the administration of partially mature DCs or compositions comprising partially mature DCs that have been HLA-matched to a patient to be treated as taught by Murphy et al. Therefore, any combination of Triozzi et al., and/or Labeur et al. with Murphy et al., do not teach or suggest each and every element of dependent claim 26.

The response has been considered but is not found to be persuasive for the following reasons:

The dendritic cells treated with GM-CSF and IL-4 taught by Triozzi et al, and as evidenced by Labeur et al appear to be the same as the claimed partially matured dendritic cells, supra.

It would have been obvious that to replace DCs obtained from the individual to be treated taught by Triozzi et al and Labeur et al with DCs that have been isolated from from a healthy individual HLA-matched to the individual to be treated, as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

New Rejection upon Review and Reconsideration

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 13-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "partially matured" in claims 1-9, 13-32 is a relative term which renders the claim indefinite. The term "partially matured" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 3, 2010

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643